EXHIBIT 2

1: J Comp Neurol 1996 Jun 24;370(2):203-30 Related Articles, Books, LinkOut

Functional fetal nigral grafts in a patient with Parkinson's disease: chemoanatomic, ultrastructural, and metabolic studies.

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A patient with Parkinson's disease received bilateral fetal human nigral implants from six donors aged 6.5 to 9 weeks post-conception. Eighteen months following a post-operative clinical course characterized by marked improvement in clinical function, this patient died from events unrelated to the grafting procedure. Post-mortem histological analyses revealed the presence of viable grafts in all 12 implant sites, each containing a heterogeneous population of neurons and glia. Approximately 210,146 implanted tyrosine hydroxylase-immunoreactive (TH-ir) neurons were found. A greater number of TH-ir grafted neurons were observed in the right (128,162) than the left (81,905) putamen. Grafted TH-ir neurons were organized in an organotypic fashion. These cells provided extensive TH-ir and dopamine transporter-ir innervation to the host striatum which occurred in a patch-matrix fashion. Quantitative evaluations revealed that fetal nigral grafts reinnervated 53% and 28% of the post-commissural putamen on the right and left side, respectively. Grafts on the left side innervated a lesser area of the striatum, but optical density measurements were similar on both sides. There was no evidence that the implants induced sprouting of host TH-ir systems. Electron microscopic analyses revealed axo-dendritic and occasional axo-axonic synapses between graft and host. In contrast, axo-somatic synapses were not observed. In situ hybridization for TH mRNA revealed intensely hybridized grafted neurons which far exceeded TH mRNA expression within residual host nigral cells. In addition, gamma-amino butyric acid (GABA)-ergic neurons were observed within the graft that formed a dense local neuropil which was confined to the implant site. Serotonergic neurons were not observed within the graft. Cytochrome oxidase activity was increased bilaterally within the grafted post-commissural putamen, suggesting increased metabolic activity. In this regard, a doubling of cytochrome oxidase activity was observed within the grafted post-commissural putamen bilaterally relative to the non-grafted anterior putamen. The grafts were hypovascular relative to the surrounding striatum and host substantia nigra. Blood vessels within the graft stained intensely for GLUT-1, suggesting that this marker of blood--brain barrier function is present within human nigral allografts. Taken together, these data indicate that fetal nigral neurons can survive transplantation, functionally reinnervate the host putamen, establish synaptic contacts with host neurons, and sustain many